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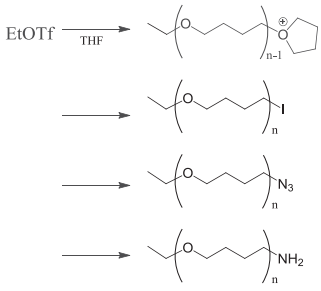
Polytetrahydrofuran (PTHF) is a very widespread polymer, which is used in numerous applications. Very frequently, its functional end groups play a key role, in that they are exploited to perform further reactions. However, only limited work is available to date on the preparation of functionalized PTHF, mostly using hazardous compounds. Here, an easy and convenient one-pot procedure is described to prepare iodo-, azido-, and amino-terminated PTHF with minimal use of hazardous chemicals. This is thought to be the first example of iodo- and azido-terminated PTHF. Additionally, a novel alternative method to obtain bromo- and cyano-terminated PTHF is reported.



1. Introduction

Polytetrahydrofuran (PTHF) is a polymer of remarkably widespread use. It has been employed in a large number of applications, such as well-defined block copolymers,[1] polyrotaxanes,[2] block copolymers for DNA delivery,[3] reactive star polymers,[4] complex matrixes for drug delivery,[5] ring-with-two-branches,[6] and 8-shaped[7] polymer topologies, a binder ingredient for propellants,[8] the backbone in supramolecular polymers for mechanochemistry studies,[9] amphiphilic co-networks,[10] topological gels,[11] and others.[12]

In the most of these applications, PTHF is further reacted with other molecules or polymers using its functional end groups, in order to obtain more complex molecular systems. Clearly, the identity of the end groups plays a fundamental role in the chemistry that can be performed with PTHF. Therefore, accessibility to a large variety of functional end groups is of paramount importance for the applicability of this polymer. Not many procedures are available in the literature to prepare functionalized PTHF or to modify the hydroxy end groups present in its most common commercial form. Various synthetic routes toward (di)amino-terminated PTHF are reported. Among them, the most exploited are the two-step procedure reported by Meijer and co-workers[13] to prepare amino-terminated telechelic PTHF, consisting of a Michael addition carried out in neat acrylonitrile, followed by reduction with borane (Scheme 1a) (93% yield reported, with a functionalization of 97%); a procedure to obtain the same product in three steps: ditosylation, *N*-alkylation of phthalimide, and hidrazinolysis (the Gabriel synthesis) reported by Takata and co-workers[2] (Scheme 1b) (54% yield reported); and a three-step procedure by Srinivasan and co-workers[14] to prepare telechelic amino-terminated PTHF, where hydrobromic acid is used as a terminating agent for the polymerization of THF, delivering dibromo-terminated PTHF, followed by nucleophilic substitution with cyanide and hydrogenation with Raney-Nickel (Scheme 1c) (functionalization of 94% reported). In another report, hexamine (HMTA) was used as the terminating agent in the polymerization of hetero-telechelic PTHF to deliver an amino terminal group.[15]

The purpose of this work is to broaden the possibilities of synthesizing end-functionalized PTHF. Here, we would like to report convenient one-pot routes to PTHF mono-functionalized with several end groups: amino, azido, iodo, bromo, and cyano.

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2. Experimental Section

2.1. General Methods and Instrumentation

Chemicals were used as received. Triphenylphosphine, ethyltriflate, sodium azide, palladium on carbon, tetrabutylammonium bromide, and 3-hydroxypropionitrile were purchased from Sigma–Aldrich; tetrahydrofuran, sodium iodide, ammonia (7 N in methanol), and 3-bromopropanol were purchased from Acros; hydrobromic acid

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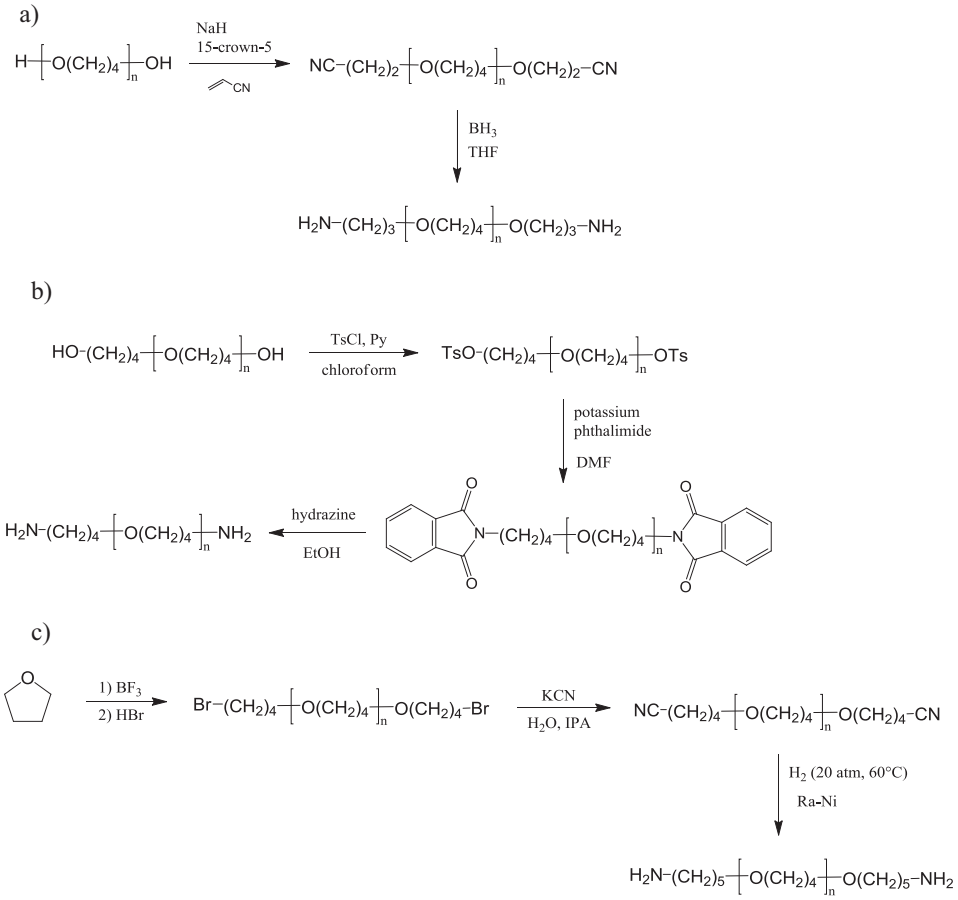


Scheme 1. Preparation of telechelic amino-terminated PTHF by: a) Meijer,[13] b) Takata,[2] and c) Srinivasan.[14]

was purchased from Merck. THF was dried before use by distillation from sodium; triphenylphosphine was added as indicator. NMR spectra were obtained using a Varian Mercury Plus operating at 399.93 MHz for ^{1}H NMR spectra and at 101 MHz for ^{13}C NMR spectra. Chemical shifts are reported in δ units (ppm) relative to the residual deuterated solvent signals of $CDCl_3$ (^{1}H NMR, δ 7.26 ppm; ^{13}C NMR, δ 77.0 ppm). The splitting patterns are designated as follows: t (triplet), m (multiplet), and br (broad).

2.2. General Procedure for the Preparation of PTHF

In a typical experiment, ethyltriflate (120 μL, 0.92 mmol) was added dropwise to THF (30 mL) with vigorous stirring at room temperature, under a nitrogen atmosphere. The mixture was stirred for 17 min, followed by the addition of the terminating agent. The degree of polymerization can be conveniently calculated by the absorption integral ratio of the terminal $-CH_3$ and the backbone in the ^{1}H NMR spectrum, and was found to be 32 on average (corresponding to $\overline{M}_n$ of ≈2400 g mol^{-1}) for this reaction time. Increasing or decreasing the reaction time afforded higher or lower molecular weights, respectively.

To precipitate the obtained PTHF, the reaction mixture was poured dropwise in water while stirring vigorously, cooled to 6 °C, and left stirring overnight. The product slowly separates as a white solid. As an alternative to cooling, the stirring can be continued for 2 d at room temperature. When the PTHF to be precipitated was carrying an amino group, NaOH 0.25 M (or higher) aqueous solution was used instead of neutral water, in order to keep the amino group deprotonated.

It is of note that in the ^{1}H NMR spectrum of the polymer, the absorption of the residual water occurs at ppm as high as 5 (and perhaps even higher is possible) rather than at the commonly observed 1.6. This is probably due to interactions with the PTHF.

2.3. One-Pot Procedure for the Preparation of Amino-Terminated PTHF

Ethyltriflate (120 μL, 0.92 mmol) was added dropwise to THF (30 mL) with vigorous stirring at room temperature under a nitrogen atmosphere, and the mixture was stirred for 17 min. Sodium iodide (555 mg, 3.7 mmol, 4 equiv.) was added in one portion to terminate the polymerization. The solution turned yellow immediately. The mixture was stirred for 1 h to form **1**. Subsequently, sodium azide (300 mg, 4.6 mmol, 5 equiv.) and water (2 mL) were added, and the mixture was refluxed overnight to give **2**. Finally, one of the following reducing agent was added, and reacted as indicated: i) Pd/C 10% (50 mg), H_2 atmosphere, overnight. The catalyst was

filtered off after the reaction was completed; ii) PPh_3 (1.7 g, 6.5 mmol, 7 equiv.), refluxed 3 h. Subsequently, the reaction mixture was poured dropwise onto NaOH 0.25 M aqueous solution (400 mL) vigorously stirred and cooled at 6 °C with continuous stirring. After 1 d, product **3** was recovered by filtration.

The process can be stopped at the iodo-terminated PTHF **1** or at the azido-terminated PTHF **2**, according to the desired end-group, by precipitating the polymer in water. The degree of polymerization can be conveniently calculated by the absorption integral ratio of the terminal $-CH_3$ and the backbone in the ^{1}H NMR spectrum, and was found to be 32 on average for this reaction time (corresponding to $\bar{M}_n$ of ≈2400 g mol^{-1}). Increasing or decreasing the reaction time afforded higher or lower molecular weights, respectively.

2.4. Conversion of Iodo and Bromo End Groups into Amino

In a pressure vial, iodo-terminated PTHF **1** (100 mg, $\bar{M}_n$ = 3800 g mol^{-1}) was added, followed by a NH_3 7 N solution in methanol (1 mL). The mixture was stirred at 90 °C for 20 h. Subsequently, the volatiles were eliminated by rotary evaporation. The amino-terminal group (**3**) was obtained in about 50% yield; 2% of secondary amine was also observed.

The same procedure was followed with the bromo-terminated PTHF **4**. Similar results were obtained, but in this case the formation of additional side products was observed.

2.5. Spectroscopic Data

1: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.49–3.32 (br, backbone + $-OC\underline{H}_2CH_3$), 3.2 (t, J = 6.98 Hz, $-CH_2I$), 1.95–1.86 (m, $-CH_2C\underline{H}_2CH_2I$), 1.69–1.55 (br, backbone), 1.19 (t, J = 7.00 Hz, $-OCH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 70.8–70.3 (backbone), 69.5 ($-O\underline{C}H_2CH_2CH_2CH_2I$), 66.0 ($-\underline{C}H_2CH_3$), 30.4–30.6 ($-OCH_2\underline{C}H_2\underline{C}H_2CH_2I$), 26.8–26.1 (backbone), 15.2 ($-OCH_2\underline{C}H_3$), 6.9 ($-\underline{C}H_2I$).

2: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.50–3.35 (br, backbone + $-OC\underline{H}_2CH_3$), 3.30 (t, J = 6.56 Hz, $-CH_2N_3$), 1.70–1.55 (br, backbone), 1.19 (t, J = 7.01 Hz, $-OCH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 70.3–70.0 (backbone), 66.0 ($-\underline{C}H_2CH_3$), 51.3 ($-CH_2N_3$), 27.1–26.1 (backbone), 15.2 ($-CH_3$).

3: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.50–3.35 (br, backbone + $-OC\underline{H}_2CH_3$), 2.74 (t, J = 6.78 Hz, $-CH_2NH_2$), 1.70–1.52 (br, backbone), 1.19 (t, J = 7.01 Hz, $-CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 70.8–70.3 (backbone), 66.0 ($-\underline{C}H_2CH_3$), 42.0 ($-CH_2NH_2$), 30.5–30.2 ($-OCH_2\underline{C}H_2\underline{C}H_2CH_2NH_2$), 26.9–25.8 (backbone), 15.2 ($-CH_3$).

4: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.52 (t, J = 5.88 Hz), 3.50 (t, J = 6.55 Hz), 3.50–3.34 (br, backbone + $-OC\underline{H}_2CH_3$), 2.12–2.05 (m, $-OCH_2C\underline{H}_2CH_2Br$), 1.71–1.52 (br, backbone), 1.19 (t, J = 7.01 Hz, $-CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 70.8–70.3 (backbone), 68.0 ($-O\underline{C}H_2CH_2CH_2Br$), 66.0 ($-\underline{C}H_2CH_3$), 32.9 ($-CH_2Br$), 30.7 ($-OCH_2\underline{C}H_2CH_2Br$), 27.1–26.1 (backbone), 15.2 ($-CH_3$).

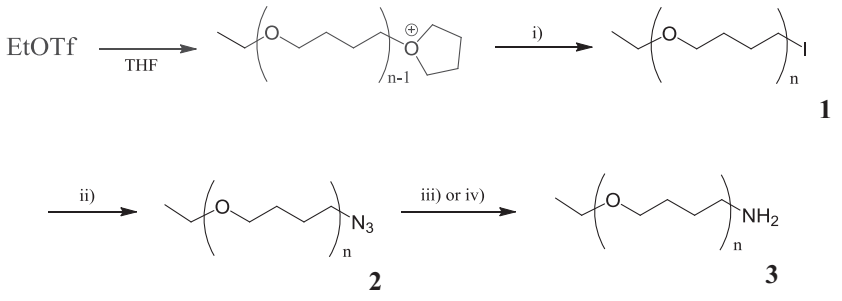
5: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.50–3.35 (br, backbone + $-OC\underline{H}_2CH_3$ + $-OC\underline{H}_2CH_2CH_2NH_2$), 2.78 (t, J = 6.84 Hz, $-CH_2NH_2$), 1.73–1.54 (br, backbone + $-OCH_2C\underline{H}_2CH_2NH_2$), 1.19 (t, J = 7.01 Hz, $-CH_3$).

6: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.60 (t, J = 12.67 Hz, $-OC\underline{H}_2CH_2CN$), 3.49–3.29 (br, backbone + $-OC\underline{H}_2CH_3$), 2.55 (t, J = 6.38 Hz, $-C\underline{H}_2CN$), 1.69–1.49 (br, backbone), 1.15 (t, J = 7.01 Hz, $-CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 117.8 (–CN), 71.1–70.3 (backbone), 65.9 ($-\underline{C}H_2CH_3$), 65.2 ($-O\underline{C}H_2CH_2CN$), 26.9–26.0 (backbone), 18.8 ($-\underline{C}H_2CN$), 15.1 ($-CH_3$).

3. Results and Discussion

Two reported procedures for the synthesis of amino-terminated PTHF consist of three steps, each requiring isolation of the product;[2,14] one of these procedures employs explosive Raney nickel (Scheme 1c).[14] In another procedure, consisting of two synthetic steps, toxic acrylonitrile is used as solvent in one of the two steps (Scheme 1a).[13] We developed a one-pot procedure for the preparation of amino mono-terminated PTHF, which, conveniently, does not require the isolation of the product after each step, and employs more inoffensive chemicals.

Sodium iodide was found to be an effective terminating agent. After initiating the polymerization of THF with ethyl triflate and waiting for the desired reaction time, an excess of NaI can be added, which yields iodo-terminated PTHF **1** quantitatively (based on ^{1}H NMR spectrum integral of $-C\underline{H}_2I$ compared with $C\underline{H}_3CH_2O-$) and in a short time (Scheme 2). Therefore, iodide anion, well soluble in the reaction mixture, is proven to be an effective terminating agent for the cationic polymerization. Subsequently, sodium azide and water can be added to convert the iodo in azido **2** via nucleophilic substitution; the addition of water is necessary to improve the solubility of NaN_3. Also this reaction proved to be quantitative. Sodium azide was found to be not effective as terminating agent, probably because of its poor solubility in the reaction mixture (the addition of water, in this case, would lead to hydroxy-terminated PTHF). To our knowledge, iodo- and azido-terminated PTHF have not been



Scheme 2. One-pot preparation of amino-terminated PTHF. i) NaI (4 equiv.), 1 h (quant.); ii) NaN_3 (5 equiv. from a 150 mg mL^{-1} water aqueous solution), reflux overnight (quant.); iii) Pd/C 10% (54.4 mg mmol^{-1} of EtOTf), H_2 atm, overnight (yield: 90%); iv) PPh_3 (7 equiv.), reflux 3 h (yield: 95%).

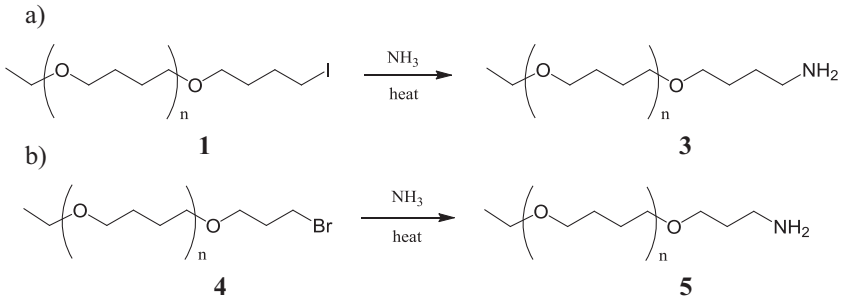
reported so far. Finally, adding palladium and putting the reaction mixture in a hydrogen atmosphere reduced the azido group to amine in 90% yield (determined by the ^{1}H NMR spectrum integral ratio of $-C\underline{H}_2NH_2$ and $C\underline{H}_3-$), resulting in polymer **3** (Scheme 2).

Triphenylphosphine was also effective in transforming the azido group in amine (the Staudinger reaction), delivering up to 95% yield (determined by ^{1}H NMR spectrum integral ratio of $-C\underline{H}_2NH_2$ and $C\underline{H}_3-$) after refluxing for 3 h. Unfortunately, triphenylphosphine proved to be difficult to eliminate.

With both hydrogenation and the Staudinger reaction, ^{1}H NMR spectroscopy analysis revealed complete conversion of the azido, albeit the yield of the amino group was somewhat lower than 100%. No side products were observed. It is still unclear why the $-C\underline{H}_2NH_2$ integrals appear lower than expected.

It should be stressed that the process can be stopped at the iodo-terminated PTHF **1** or to the azido-terminated PTHF **2**, according to the desired end-group.

The possibility to obtain amino-terminated PTHF **3** directly from the iodo-terminated polymer **1** was explored as well (Scheme 3a). When **1** was reacted for 20 h with ammonia at 90 °C (a pressure vial was used), about 50% of the product was obtained. However, ^{1}H NMR spectroscopy analysis revealed the formation of a small quantity of secondary amine (ca. 2%) coming from a double reaction of ammonia; shorter reaction times and lower temperatures were not sufficient to achieve complete conversion. Other unidentified impurities were also observed. Starting from the bromopropyl-PTHF **4** (Scheme 3b), delivered similar results.

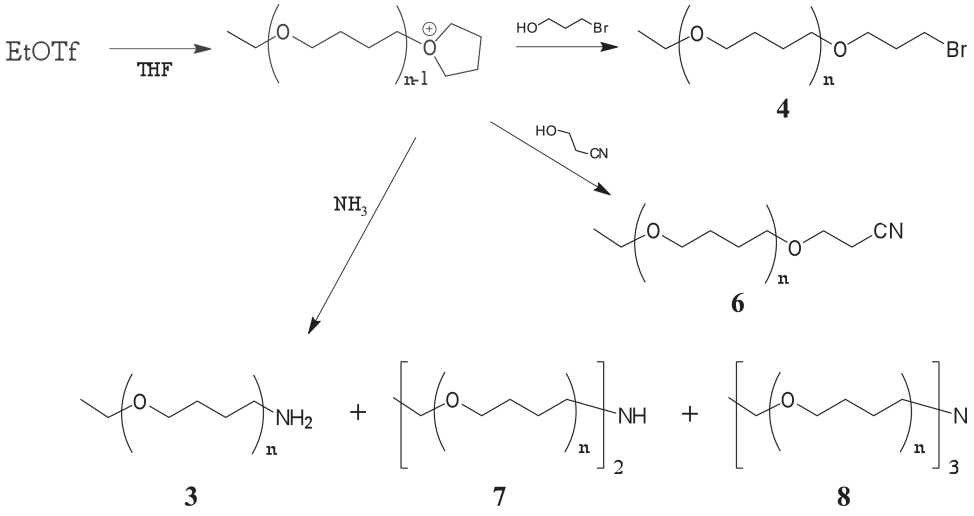


1 3 4 5

Scheme 3. Preparation of the amino-terminal group from iodo and bromo. Ammonia was used in a 135-fold excess from a 7 N solution in methanol. Conditions: 90 °C, 20 h; yield: about 50%.

Hydrobromic acid has already been reported as terminating agent in the preparation of bromo-terminated PTHF.[14] In our experience, the use of hydrobromic acid causes a fragmentation of the chains, as indicated by the remarkably lower tendency of the product to precipitate in water. We observed the same effect with tetrabutylammonium bromide. Better results could be achieved using 3-bromopropanol (5 equiv.) as terminating agent, which afforded bromopropyl end group in about 70% yield on the basis of ^{1}H NMR spectroscopy analysis (some side products were also visible). When 3-hydroxypropionitrile was employed (5 equiv.), the yield of the cyano end group was as high as 90%. The obtained PTHF **6** can eventually be reduced to obtain amino-terminated polymer as previously reported[13,14] (Scheme 4).

Ammonia was tested as terminating agent, in an attempt to achieve amino-terminated PTHF in one single step. A NH_3 7 N solution in methanol was used in two different amounts: 15 and 33 equivalents with respect to the initiator, and was added quickly in one portion. The mixture was stirred at room temperature overnight to let the reaction complete. As revealed by ^{1}H and ^{13}C NMR spectroscopy, product **3** was obtained, but in both cases



4 6 3 7 8

Scheme 4. Termination by 3-bromopropanol (5 equiv.), 3-hydroxypropionitrile (5 equiv.), and ammonia.

also the unwanted secondary (**7**) and tertiary (**8**) amines were formed (Scheme 4).[16]

Based on the ^{1}H NMR spectroscopy absorption integrals, the primary/(secondary + tertiary) ratio was 4.5 and 2.1 with 33 and 15 equivalents of ammonia, respectively. As expected, the formation of secondary and tertiary amines is lower when more ammonia is used. It can be envisioned that using neat ammonia, possibly in an even larger excess, will further reduce these side products.

4. Conclusion

A convenient one-pot procedure for the synthesis of mono amino-terminated PTHF has been developed. In this procedure, no explosive or volatile toxic compounds are used. Moreover, iodo- and azido-terminated PTHF can also be easily isolated from this procedure in quantitative yields, and used for different transformations. For example, azido-terminated PTHF could be used for click chemistry. Ammonia can also be used as terminating agent to give directly amino-terminated PTHF, but the formation of secondary and tertiary amines may be unwanted. Additionally, we have shown that 3-bromopropanol and 3-hydroxypropionitrile are efficient terminating agents, which can deliver bromo- and cyano-terminated PTHF in very high yields.

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